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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/712,332	11/13/2003	David L. Wolf	MPI90-002CP2DV1CNBCN3M	1297

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,332	WOLF ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 6-12* is/are pending in the application.

4a) Of the above claim(s) *6-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4, and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 2, 4, and 6-12 are pending in the current application.

Claims 3 and 5 have been canceled, and claims 6-12 added, as per applicant's amendment received December 15, 2004.

Applicant's election without traverse of Group I, claims 1, 2, 4, and 6-12, drawn to a blood factor composition, and the elected species "activated protein C", in the reply filed on December 15, 2004 is acknowledged.

Applicant's amendment to the claims received December 15, 2004 necessitated a further species election. A telephone interview was conducted with Tracy M. Sioussat on January 12, 2004 to elect a species of inhibitor from the following: benzamidines, substituted benzamidines, Kunitz class inhibitors, and antibody or antibody fragments. An election of substituted benzamidines was made without traverse.

Claims 6-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species.

Claims 1, 2, 4, and 10-12 are under examination as they read on the elected species of activated protein C and substituted benzamidines.

2. Applicant is reminded to amend the first line of the specification to indicate the identity and relationship of all applications from which priority is claimed under 35 USC 120 in relation to the instant application, and to update the current status of all applications identified elsewhere in the specification.

It is noted that the instant application is not in sequence compliance. Applicant is required to review the instant application for compliance with the requirements of applications which contain sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821-1.825. If the instant application does not have an appropriate SEQ ID NO: for each disclosed sequence, then Applicant must comply with the Sequence Rules as set forth in 37 CFR 1.821-1.825. Examples of sequences not identified by SEQ ID numbers can be found on page 34, lines 14, 17, and 32. Appropriate correction is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Priority

3. Applicant's claim for priority to application 07/578,646 filed 09/04/1990 (US patent no. 5,278,144), application 07/808,329 filed 12/16/1991 (abandoned), and application 08/249,777 filed 05/26/1994 (US patent no. 5,597,799) are acknowledged. However, the examiner has determined that the appropriate filing date for the instant claims is that of application 08/268,003 filed 6/29/1994 (US patent no. 5,583,107) since this is the first application that discloses compositions comprising blood factors, including activated protein C, that are transiently inactivated. Earlier applications only disclose compositions wherein the blood factor Xa is permanently inactivated. Therefore, the earliest disclosure that supports the instantly claimed invention is that of application 08/268,003. As such, the effective filing date for the instant claims in relation to the prior art is that of application 08/268,003, namely 6/29/1994.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 recites the limitation "modified activated protein C". There is insufficient antecedent basis for this limitation in the claim since it is dependent upon claim 1 which recites only a "transiently inactive modified activated protein C". Amending claim 12 to recite a transiently inactivated modified activated protein C would obviate this rejection.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 4, and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant has claimed a composition in which activated protein C is transiently inactivated by the substituted benzamidine 1,2-bis(5-amidino-2-benzofuranyl)ethane. Tidwell et al. described this substituted benzamidine as a preferential inhibitor of Factor Xa since the inhibitor's affinity for Xa was 26 times greater than for thrombin (Thrombosis Research, 1980, 19: 339-349, see entire document, particularly the abstract and the last sentence of the first paragraph of the results section on page 341). Factor Xa and thrombin have different biological activities based upon their specificity of binding even though they are related serine endopeptidases (Tidwell et al., see particularly the first paragraph of the discussion section that begins on page 345).

Activated protein C is also a serine endopeptidase, but its biological activity is to degrade blood factors Va and VIIIa, while the activity of Xa is to form thrombin from prothrombin, and the activity of thrombin is to cleave fibrinogen to form fibrin and fibrinopeptides A and B (see particularly the data concerning activated protein C (EC 3.4.21.69), Xa (EC 3.4.21.5) and thrombin (EC 3.4.21.5) obtained from the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (NC-IUBMB) at www. Chem..qmul.ac.uk/iubmb/enzyme/EC3/4/21/). Andrews et al. studied the inhibition of the related serine endopeptidase enzymes trypsin, thrombin, plasmin and complement component C1s by substituted benzamidines (J Medical Chemistry, 1978, 21:1202-1207, see entire document, particularly the abstract). Andrews et al. observed that the inhibition of these related enzymes by substituted benzamidines was not always predictable (see particularly the last full paragraph of page 1206 and the final sentence of the discussion section found on page 1207).

Applicant has generically stated that substituted benzamidines are useful as blood factor inhibitors, and has specifically stated that 1,2-bis(5-amidino-2-benzofuranyl)ethane is an inhibitor of Xa, on page 17, lines 6-18 of the specification. However, no specific guidance or working examples of inhibitors of activated protein C appear to be provided. Since 1,2-bis(5-amidino-2-benzofuranyl)ethane is recognized in the prior art as a strong inhibitor of factor Xa but 1,2-bis(5-amidino-2-benzofuranyl)ethane does not appear to be recognized in the prior art as an inhibitor of activated protein C, since the prior art teaches that the inhibition of related enzymes by substituted benzamidines is unpredictable, since the specification provides no working

examples concerning the inactivation of activated protein C with and inhibitor, and since the guidance in the specification concerning inactivation using benzamidine inhibitors is directed toward blood factors in general and not activated protein C specifically, a person of skill in the art would not be able to make and use a composition comprising activated protein C that has been transiently inactivated by substituted benzamidines as a group or a composition comprising activated protein C that has been inactivated specifically by the substituted benzamidine 1,2-bis(5-amidino-2-benzofuranyl)ethane.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 4, 11, and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Sturzebecher et al. (Thrombosis Research, 1993, 69:533-539, see entire document).

Sturzebecher et al. teach the inhibition of activated protein C by benzamidine derivatives (see entire document, particularly the abstract). The benzamidine derivatives used are indicated in Tables 1, 2, and 3, and the structure of these inhibitors is consistent with that of substituted benzamidines as disclosed on page 17, lines 6-18 of the specification. When these benzamidine derivatives were added to a solution

containing activated protein C, a composition consisting of a transiently inactivated activated protein C comprising a substituted benzamidine in the pharmaceutical excipient of a Tris-buffered solution was created (see particularly the Materials and Methods section on page 534). This pharmaceutical composition contained transiently inactivated activated protein C because the competitive binding of benzamidine-derived inhibitors is reversible (see particularly the last full sentence on page 533). Such compositions have utility as antithrombotic agents in the treatment of shock and stroke (see particularly the fourth line from the bottom on page 537).

It is noted that the claim recites the use of a modified blood factor that has little or no enzymatic activity. The specification discloses many ways to modify blood factors, such as acylation, glycosylation, and changes to the primary amino acid sequence of a blood factor, but the specification does not define or clearly limit the terms "modified blood factor" or "modified form of a blood factor" to refer to only one type or manner of modification. Claim 1 limits the term "modified blood factor" to mean little or no enzymatic activity. The addition of a substituted benzamidine transiently inhibits activated protein C, thus making it a modified blood factor that has little or no enzymatic activity consistent with the teachings of the specification and the claims.

Therefore, the prior art anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (US Patent no. 4,604,285, see entire document) in view of Eichel et al. (US Patent no. 5,026,559, see entire document).

Smith et al. teaches a pharmaceutical composition comprising activated protein C that has been acylated in its active site that is useful in treating thrombosis (see entire document, particularly the abstract, column 1, lines 4-7, column 2, lines 59-63, and claims 1-8). The acylation is removed by serum proteases *in vivo* to regenerate the active enzyme, and this modification of activated protein C by acylation extends its half-life in serum (see particularly column 1, lines 7-30 and claim 1). Smith et al. teach that activated protein C modified by acylation can be administered to a patient in pharmaceutical compositions that comprise pharmaceutically acceptable carriers (see

particularly column 2, lines 29-34). Smith et al. do not teach the use of polyethylene glycol conjugation or microencapsulation.

Eichel et al. teach pharmaceutical compositions prepared by microencapsulation (see entire document, particularly the abstract). Such compositions are advantageous because they provide for the delayed, gradual, long-term release of a therapeutic drug that is delivered orally since the coating that encapsulates the drug must be first solubilized by digestive fluids before the drug is available for absorption by the body (see particularly the abstract and column 1, lines 6-62).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to microencapsulate the modified activated protein C taught by Smith et al. using the microencapsulation techniques taught by Eichel et al. for the advantage of making a pharmaceutical composition that provides for the gradual long-term release of an orally administered drug.

11. No claims are allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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